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β-CARBOLINES, PSYCHOACTIVE COMPOUNDS IN THE MAMMALIAN BODY

PART II: EFFECTS

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ABSTRACT

The biochemical and the pharmacological effects of β-carbolines in animals and man are reviewed. Biochemical studies have revealed β-carbolines' several actions, including inhibition of MAO-A, competitive inhibition of 5-HT uptake, general inhibition of Na^+ dependent transports, binding to benzodiazepine and opiate receptors and probable action on dopamine receptors, which may all participate to a variable degree in the actions of different β-carbolines. Many early in vivo studies, however, have concentrated on some harmala alkaloids, particularly harmaline or harmine. The effects of β-carbolines in man are compared in this review with the symptoms of alcohol withdrawal. However, no human studies have been reported with those tetrahydro-β-carbolines shown to occur in human body in normal conditions or after alcohol intake. To prove any connections of β-carbolines with the withdrawal syndromes or other neurological and psychiatric diseases means that these compounds have to be shown to have abnormal central nervous system concentrations in these diseases.

The physhiological role of β-carbolines has yet to be shown. They may act as neuromodulators and some, especially 6-methoxytetrahydro-β-carboline, may have an endocrinological function. It has been suggested that some β-carbolines act as the physiological ligands (agonists) of the benzodiazepine receptors, but the physiological β-carbolines so far known seem to have other effects, such as the inhibition of MAO-A or 5-HT uptake in low concentrations.

KEY WORDS: β-CARBOLINES; HARMALA ALKALOIDS; TRYPTOLINES; HALLUCINOGENS; ALCOHOL; EFFECTS

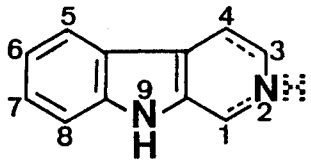
INTRODUCTION

The recent identification of some β-carboline derivatives in human body (see part I; 6) has increased interest in their effects on and possible role in physiological and pathological conditions. Considerable ethnopharmacological knowledge exists about the use of plants and potions containing β-carbolines (see part I and 48). However, only experimental studies in vivo and in vitro with known doses of known compounds can provide knowledge of value for the evaluation of the effects, modes of action and role of different β-carbolines.

Such experiments in man are few but several special actions and biochemical effects of β-carbolines have been extensively studied in animals in vivo and in vitro. On the other hand, biochemical studies, including some recently found actions on specific membrane receptor sites, may give major clues to the mode of action of these compounds and on their physiological significance.

Although we wanted to describe particularly the effects of those β-carbolines which are or may be formed in the mammalian body, more information is available from studies using nonphysiological but naturally occurring harmala alkaloids. Many effects of β-carbolines are common for several derivatives, the differences being quantitative. So we have not described the diverse effects of β-carbolines drug by drug but instead effect by effect. However, the differences in the ring structures of 1,2,3,4-tetrahydro-β-carbolines (THBCs), 3,4-dihydro-β-carbolines (DHBCs) and β-carbolines (BCs), as well as the presence of different radicals in the ring also cause qualitative differences in the effects, particularly in vivo, where the drug concentrations cannot be raised as high as in some in vitro studies.

For the names and numbering of different β-carbolines we refer to Fig. 1 and to the part I (6); in addition to the shortened systematic names we also use two common alkaloid names, harmaline (7-MeO-1-Me-DHBC) and harmine (7-MeO-1-Me-BC), without giving the shortened chemical name in parentheses every time.



1. The skeleton of β-carbolines and the mbering used in this paper. The tetrahydro-β-rbolines (THBCs, tryptolines, tetrahydronorhar-ne derivatives) have the dotted H-atom, the -dihydro-β-carbolines (DHBCs) have a 1—2 uble bond and the »fully aromatized» β-carbo-es (BCs) have both the dotted double bonds. her naming systems include a complicated ridо[3,4-b]indole naming, common alkaloid mes and a more general naming system derived m harman(e) (1-Me-BC) and norharman (BC). ese also use the same numbering as given ove. In the tryptoline names made for THBCs Me-THBCs are called methtryptolines) the mbering starts from the pyridine nitrogen (N-2). o numbering systems starting from the pyr-e-nitrogen also occurred in earlier literature, but these systems are not used at present.

OCHEMICAL EFFECTS

ibition of monoamine oxidases

dies dealing with inhibitor activity of rbolines on monoamine oxidase (EC 3.4., MAO) can be divided in two groups. the earlier investigations (before 1970) the ency of β-carbolines was underestimated, ce at that time the biochemistry of MAO s only marginally understood. Two forms this enzyme, designated MAO-A and O-B by Johnston (82), are known, the tive activities of these two forms varying tly in different organs and species (87, , 170). MAO-A acts on 5-hydroxytrypt-ne (5-HT) and noradrenaline (NA), where-MAO-B acts on benzylamine and β-phe-thylamine (PEA). Dopamine (DA), tryptamine and tyramine seem to be the preferred strates for both MAO-A and MAO-B (129). As early as in 1958, using 5-HT as the strate for liver enzyme, Udenfriend and orkers (180) demonstrated that harmaline MeO-1-Me-DHBC) and related compounds re potent inhibitors of MAO. This obser-ion was verified by Pletscher et al. in 0 (137). During the years 1966—1970 the ucture-activity relations have been exten-ly clarified using tryptamine or tyramine substrate for liver MAO. Ho reviewed e papers in 1972 (71). Later Meller et al. 5) and Buckholtz and Boggan (34, 35) re-ted that β-carbolines are potent and selec-MAO-A inhibitors. In fact, harmaline been used as a model substance for a selective MAO-A inhibitor (58, 121). The major binding sites of harmaline seems to be in MAO-A, since its regional distribution correlates with the activity of MAO-A and it can be released by other MAO-A inhibitors (130).

The inhibitory effect of β-carbolines on MAO has been shown to be reversible and usually competitive (71, 180) — only the inhibition caused by 9-Me-THBC has been reported as being noncompetitive (115). In general, the unsaturated β-carbolines (DHBCs and BCs) are more potent inhibitors than the corresponding THBCs for MAO both in the liver and in the brain (35, 71, 110). Methyl substitutions in the β-carboline skeleton (positions 1, 2, 3 and 4, see Fig. 1) seem to lower the inhibitory activity. A methyl-group in the indole nitrogen, however, strongly increases inhibition (35, 71, 75), the resulting THBC compound being in this respect as potent as the corresponding aromatic compound (74). A hydroxyl at C-6 or C-7 or a methoxy substituent at C-6 either slightly decreases or has no effect on inhibitor activity (35, 110, 115). The methoxy substituent at C-7 seems to increase the MAO-A potency quite significantly (35, 180), although an opposite observation has been reported for the mixed MAO activity mainly MAO-B (110).

In these in vitro investigations the IC_{50} values vary widely depending on the substrate, the enzyme source and the assay method used. In the earlier experiments the enzyme source was rat or bovine liver (71, 137, 180), but the activity of MAO-B in the liver of these animals is greater than that of MAO-A, the opposite being so for brain tissues (170). Thus the IC_{50} values obtained with liver MAO using 5-HT as substrate are higher than those obtained with brain MAO. The IC_{50} of harmaline, the most potent MAO-inhibiting β-carboline, is about 10^{-8}M in the brain, while the comparable value in the liver MAO is about 10^{-6}M (35, 180) and IC_{50} values of about 10^{-4}M were obtained with tryptamine or tyramine as substrates (110).

The results obtained in vivo or ex vivo parallel quite closely those obtained in vitro (35, 115, 137, 180). The maximum MAO inhibition is observed after 2—3 hours (35, 180), the inhibition ending within 6 hours after administration of β-carboline (180). However, Sparks and Buckholtz reported in 1981 (169), that MAO-A inhibition caused by 6-MeO-THBC rises to a maximum at 1 h (56 %), decreasing to 30 % at 12 h, and ending at 24 h.

Effects on other enzymes

Apart from MAO, the effects of β-carbolines on enzymes have not been extensively investigated. However, the inhibitory activity of harmine (7-MeO-1-Me-BC) on rat, monkey and human liver N-acetyltransferase (EC 2.3.1.35) was reported by Schloot et al. as early as in 1969 (152), an observation later verified by Wright et al. (187) using livers of rats and golden hamsters. Harmine seems to be a quite potent N-acetyltransferase inhibitor, the IC_{50} value being about 10^{-5}M.

The influence of some β-carbolines on cholinesterase (EC 3.1.1.7.) has also been described (132). Quite low concentrations inhibit this enzyme, the IC_{50} value of 1-Me-BC (harman) and some other β-carbolines being about 10^{-5}M.

Harmaline has been shown to activate guanylate cyclase (168) and to inhibit (Na^+-K^+)-ATPase (see later).

Harmine was not found to alter the activities of dopamine-β-hydroxylase (EC 1.14.17.1.), tyrosine hydroxylase (EC 1.14.16.2.) and dopa-decarboxylase (EC 4.1.1.28.) (59). 1-Me-THBC inhibits alcohol dehydrogenase (EC 1.1.1.1., 116).

General effects on transport mechanisms

Sodium transport and sodium-dependent transport. Several studies have shown that harmaline inhibits the transport of Na^+ and Na^+-coupled uptake of d-glucose and neutral amino acids and peptides. In some studies other β-carbolines were also shown to have similar effects but so far as we know more comprehensive structure-activity studies have not been carried out. These effects of harmaline were shown in intact intestinal preparations (155, 156, 157) and by using many other tissues and methods e.g. the kidney micropuncture (151), slices of kidney cortex (156), neural tissue of mammals (37), separated intestinal and renal brush border and basolateral membrane vesicles (13, 15, 80), as well as amphibian skin preparations (45).

The inhibition of sodium-dependent sugar and amino-acid uptake by harmaline was first found in slices of guinea pig small intestine (155), and later in other biological membranes studied. Therefore the inhibition with harmaline has become a method to demonstrate the sodium dependence of certain transport systems, e.g. the dipeptide transport in monkey intestine (54).

The mechanism of the β-carboline action on Na^+-transport and Na^+-dependent transport is not clear. Harmaline inhibits (Na^+-K^+)-ATPase (37, 143) competing for its [illegible] sites (13, 14, 15) and seems to interact [illegible] Na^+-binding-sites of various carrier [illegible] plexes (157). Harmaline has been reported [illegible] inhibit (Na^+-K^+)-ATPase and sodium-dependent amino acid transport without affecting the ouabain-insensitive ATPase or sodium-independent amino acid uptake (142). In amphibian skin harmaline also has a vasopressin-like activating effect on water transport which is possibly connected with effects on cyclic nucleotides (45).

Chloride transport. The benzodiazepine-GABA receptor complex is thought to regulate the Cl^- channel (40), and those β-carbolines which bind to benzodiazepine receptors antagonize the Cl^--channel opening effects of benzodiazepines and GABA. The binding of β-carbolines on benzodiazepine receptors seems to be less influenced by Cl^-ion than that of benzodiazepines (25, 27). Little is known of the direct effects of β-carbolines on Cl^-transport or on the transport of other ions except for sodium.

Transport of specific amino acids. The above-mentioned inhibition of Na^+ dependent transport has been demonstrated using quite high β-carboline concentrations. It remains to be shown how far this Na^+-site inhibition explains the transport inhibition of specific amino acids like the uptake of GABA (140, 182). Vargas and Erlij (182) have shown that a rather high concentration of harmaline is needed outside the brain synaptosomes to block trans-stimulation of GABA on the efflux of newly uptaken [^{3}H]GABA.

It is not known whether inhibiting precursor amino acid uptake can explain a decrease in striatal dopamine concentration and in the rate of dopamine synthesis from L-dopa after harmaline administration to cats (139, 161). The concentration of 5-HT increased and the formation of 5-HT from 5-HTP did not fall. After 6-MeO-THBC administration 5-HT synthesis from 5-HTP and tryptophan increased somewhat (76), suggesting either enzyme activation or an increase in the uptake of these amino acids. A decrease of brain dopamine was also sometimes observed after 6-MeO-THBC. On the other hand, amine uptake by neurones and the permeability of intracellular vesicles may also be influenced through Na^+-transport. Thus as already found in the early stage, harmaline inhibits the ATP-Mg^{++}-dependent adrenaline uptake into isolated medullary vesicles of

drenals, and harmaline induces a decrease the output of noradrenaline from the per-sed heart preparation (79).

hibition of the uptake and release of mine neurotransmitters

atelets, synaptosomes and brain slices. Inhi-tion of 5-HT uptake by β-carbolines has rgely been studied in rat brain synapto-mes (89, 147, 179) and in human, ox and bbit platelets (4, 10, 96, 178). The uptake DA and NA are often simultaneously stud-d and one study includes results on the ptake of histamine (178), and another on the ptake of GABA and choline (149).

The uptake of 5-HT is effectively in-bited by THBCs, 6-OH-THBC being the st active in synaptosomes (89, 147) and MeO-THBC in platelets (10), but only the tter slightly exeeded the potency of 5-HT 1-Methylated THBCs and all DHBCs and Cs studied were less potent.

All β-carbolines also inhibited DA and NA ptake in some degree but were far less po-nt inhibitors than the parent amines them-ves (10, 89, 147, 179). The structure-affin-relations have been more thoroughly de-ibed by us in recent papers (10, 89). Effects the uptake of histamine by platelets (178) well as GABA and choline by synapto-mes (149) were small. While the inhibition Na^+ sites may influence the transport of urotransmitter amine uptake with high arboline concentrations, inhibition of the ake of 5-HT by the most potent THBCs 6-MeO-THBC occurs with lower concen-tions and is clearly competitive with 5-HT , 89, 117). Only the effect of 6-OH-1-Me-BC in one study has been described as ncompetitive for 5-HT (117).

Only in high concentrations as β-carbolines rease spontaneous release of 5-HT or pamine (4, 42, 114, 149). However, THBC been shown to increase K^+-induced 5-HT-ease but to inhibit K^+-induced dopamine ease (150).

ntracellular vesicles. Slotkin and cowork-(59, 163, 164, 166) have studied the ef-ts of β-carbolines on the uptake of [^{3}H]-adrenaline by the intracellular vesicles m rat adrenals and rat brain synaptosomes. both β-carbolines were effective compe-ve inhibitors of NA uptake, some being re effective than noradrenaline itself. The ect was considered to be reserpine-like serpine also has a β-carboline structure). ructure-activity studies showed that 7-me-thoxy-group is important. The potency de-creased in the order 2-methylharmine (6-MeO-1,2-dimethyl-BC) > harmaline > har-mine > harmol (7-OH-1-Me-BC) > harman (1-Me-BC) > norharman (BC) > 6-methoxy-harman (6-MeO-1-Me-BC). The first three IC_{50} values were less than 0.1 μM, the last one more than 1 μM. No THBCs were studied.

The effects of β-carbolines on 5-HT vesicles and on intracellular 5-HT binding are poorly known. The differences in the intracellular distribution of 5-HT and 6-MeO-THBC in our study (4) suggest that they do not compete for intracellular binding sites. Furthermore, only in very high concentrations did 6-MeO-THBC inhibit the slow rate uptake and binding of 5-HT by rabbit blood platelets in vitro, while smaller concentrations ($10^{-6} - 5 \times 10^{-5}$ mol/l) slightly increased 5-HT binding. This corresponds with the finding that in rats 6-MeO-THBC increased 5-HT concentration, especially in the particular fraction of brain (76). Furthermore, according to the preliminary results of Tamis and Buckholtz (33), 6-MeO-THBC in low concentrations also increases 5-HT binding by the (intracellular?) serotonin binding protein of rat brain, while a high concentration (10^{-4} mol/l) strongly inhibits it. The mechanism of the increased intracellular 5-HT binding is unknown.

Effects on transmitter amine concentrations

As described above and later in this review, the β-carbolines are MAO inhibitors and show other interactions with neurotransmitters in vitro, particularly with 5-HT. Thus it is natural that β-carbolines also have an effect on transmitter amine levels in vivo. In 1958 Udenfriend et al. (180) reported an increase in the concentration of 5-HT in rat brain after systemic administration of harmaline. Since then many investigators have confirmed this observation for several β-carbolines (3, 31, 32, 42, 76, 112, 137, 139, 147). The elevation of brain NA (137) and DA (75) levels by some aromatic β-carbolines has also been reported. On the other hand, a decrease both in the striatal DA and its metabolite homovanillic acid after repeated administration of harmaline has been described (139). However, most of the THBCs, particularly 6-MeO-THBC, and also harmaline, have been shown to increase the level of 5-HT, but not that of NA and DA in the brain (31, 32, 42, 76, 112, 147). Provided that the earlier observations are valid, the increase of NA levels produced by the aromatic β-carbolines may be due to the

inhibition of MAO rather than to an inhibition of uptake, as NA is like 5-HT the substrate for MAO-A and the aromatic β-carbolines are rather weak uptake inhibitors. Ho (72) has pointed out that the decreasing effect of harmaline on striatal DA may be due to its effects on the storage of the amine in vesicles. Harmaline may also affect the cell-uptake of the precursors L-dopa and tyrosine. The possibility of decreased activity of dopa-decarboxylase was excluded (59, 94).

The concentration of brain 5-hydroxyindoleacetic acid (5-HIAA) has been shown to fall after the administration of β-carbolines (31, 32, 33, 42, 147), finding which also suggests that β-carbolines may act in vivo, at least in part, by an inhibition of MAO. On the other hand, participation of β-carbolines in the control of 5-HT synthesis is not excluded. Uptake inhibition may, however, be the major mechanism by which many β-carbolines increase 5-HT concentrations in the synaptic cleft. The high selectivity of some THBCs, at least in small doses, in increasing 5-HT concentration may result from the combination of selective MAO-A inhibition, selective inhibition of 5-HT uptake, and their own selective uptake into 5-HT neurones, which allows them to inhibit brain MAO effectively only in 5-HT-neurons.

Effects on specific binding sites (receptors) of neurotransmitters and -modulators

β-Carbolines are bound with variable affinity, at least by the sodium sites in ion transport (as discussed above), by benzodiazepine binding site in benzodiazepine-GABA receptor complex, by specific opiate binding sites, the uptake sites and probably also the acting receptor site of 5-HT and catecholamines, which all might take part in the action of β-carbolines.

Benzodiazepine binding sites. The competition of β-carbolines with benzodiazepines (BZs), for their specific binding sites in rat brain synaptosomal membranes (BZ recognition sites in the BZ-GABA receptor complex) (40) has been described by several research groups almost simultaneously (7, 26, 131, 141, 146). Braestrup and coworkers (26) tried to extract the natural ligand of BZ receptors from brain tissue and from 1800 l of human urine with acidic ethanolic solution and found as an artifact ethyl-BC-carboxylate (see part I), a very potent inhibitor of specific binding of [^{3}H]flunitrazepam. Some other β-carbolines they studied showed weaker effects. At the same time both Rommelspacher et al. (146) and our group (7) were mapping the possible mode of actions of the natural β-carbolines, and could similarly show that BCs and, with a weaker affinity, DHBCs have a significant affinity to the specific BZ binding sites. Compounds with a strong electrophilic group, as well as all THBCs studied, show practically no affinity. While methoxy group is prohibitive in the 7-position (7, 146), it does not seem to prohibit in the more physiological 6-position (7). Robertson (147), when looking for the mechanism of harmaline tremor, found the affinity of this DHBC derivative to BZ receptor sites.

Ethyl-, methyl- and propyl-BC-carboxylates are among the most potent competitors of [^{3}H]flunitrazepam. The competition and the binding properties have also been demonstrated with [^{3}H]propyl-BC carboxylate as the ligand (27). When comparing with the binding of BZs, β-carbolines have a higher affinity to the »cerebellar» type than to the »hippocampal» type BZ receptors (27, 131).

The binding of [^{3}H]propyl-BC carboxylate is also increased by GABAergic agents and other drugs that increase the specific binding of BZs. In addition to the opposite actions of β-carbolines with BZs (see later) some binding properties (25) also suggest that β-carbolines act as agonists and BZs are antagonists. β-Carbolines antagonize the effect of diazepam on functional GABA-receptors (120) but no binding of β-carbolines on specific GABA binding sites have been seen by us or others. It remains to be shown whether in »GABA/BZ modulines» (natural inhibitors of BZ and GABA binding) (40) any tryptophan part has formed a β-carboline structure. On the other hand, to be active it should not have a THBC structure but, instead, a DHBC or a BC structure. It is possible to form the latter as an artifact when trying to separate these »modulines».

5-HT receptor sites. The apparent binding of some β-carbolines on the acting 5-HT receptors has been repeatedly shown indirectly in vivo and in smooth muscle and other organ preparations, although some of the effects can be explained by the changes in extracellular amine concentrations. Anti-5-HT-effect has also been occasionally found. 6-MeO-THBC seems to be a partial agonist of 5-HT in rat stomach preparation (3), with the agonistic effect about 1/500—1/1000 of that of 5-HT. A ratio of 1/600 has been described from 6-OH-1-Me-THBC and 5-HT

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Direct binding studies have indicated the binding of β-carbolines with a variable affinity to specific 5-HT sites in brain membranes (e.g. ethyl-BC-carboxylate less than 1/100 of the affinity on BZ binding sites) (25). Actions or binding on 5-HT_1 and 5-HT_2 receptors have not been clarified.

Dopamine receptor sites. No competition of any β-carbolines with dopamine for its receptor sites have been demonstrated. The lack of binding of ethyl- and propyl-BC-carboxylates has been reported (27). Also, in our preliminary studies (Airaksinen and Saano) 6-MeO-1-Me-DHBC had no effect on the specific binding of [^{3}H]apomorphine. Many β-carbolines however, show antagonistic effects on dopaminergic actions for example, harmine (184) and THBC (133, 145) decrease apomorphine-induced hypermotility and stereotypies in rats; 6-MeO-THBC decreases the motility and group toxicity of amphetamine in mice (3); and several β-carbolines, particularly 6-MeO-1-Me-DHBC, decrease apomorphine and phenylethylamine stereotypies in rats (84). It is not known if these changes are due to the action on dopamine receptors (133) or to the indirect antagonistic action of the increased serotonergic and GABAergic effect. However, the apomorphine antagonism does not correlate with the known inhibition of 5-HT uptake. Instead, some correlation with monoamine oxidase inhibition or with the binding to the benzodiazepine binding sites may be found.

Opiate receptors. Our recent study (7, 8) showed that 6-OH-1-Me-THBC and some other β-carbolines with CH_3O- or OH-group in 6- or 7-positions have a significant affinity to the specific binding of [^{3}H]dihydromorphine in rat brain, while the β-carbolines without those radicals had practically no affinity. Our preliminary results with similar affinity to [^{3}H]dihydromorphine and [^{3}H]-naloxone binding suggest that β-carbolines could be partial agonists of μ-receptors; the affinity to enkephalin binding site seemed to be variable (Airaksinen et al., unpublished).

Other receptors. Harmala alkaloids, harmaline (1-Me-BC), harmine (7-MeO-1-Me-BC), harman (BC), harmaline (7-MeO-1-Me-DHBC), harmol (7-OH-1-Me-BC) and harmalol (7-OH-1-Me-DHBC) all inhibit the transmission at a glutamate-mediated insect neuromuscular synapse in the locust Schistocerca gregaria. They have some presynaptical effect but the major site of action seems to be the postsynaptic glutamine receptor (46). It is not known whether the β-carbolines have any significant effect on the glutamate receptors in mammalian brain.

1-Me-BC has been found to bind significantly to muscarinic receptors, causing 40—50 % inhibition of [^{3}H]quinuclidinyl benzilate binding at 5×10^{-5}M, while THBCs were practically inactive (132).

Effects on mutagenesis

The study of mutagenic and carcinogenic properties of β-carbolines has been stimulated by the discovery of two β-carbolines, harman (1-Me-BC) and norharman (BC), in tobacco smoke (138), in charred meat and in routinely prepared Japanese food (172). The major mutagenic principals in the pyrolytic products of tryptophan (171) and proteins (109, 124) may be γ-carbolines. In addition, a significant decrease of total mutagenic activity in a mixture containing charred tryptophan has been observed after removal of harman and norharman from the mixture (171). On the other hand, the addition of norharman and harman, the major products in the pyrolysis of tryptophan, to a reaction mixture containing rat liver enzymes and a chemical mutagen produced a significant increase in mutagenity by the Ames assay (108, 125). Harman and norharman have been claimed to enhance the mutagenic activity of several mutagens, including benzo(a)pyrene (BP) and two γ-carboline derivatives, 3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole (Trp-P-1) and 3-amino-1-methyl-5A-pyrido[4,3-b]indole (Trp-P-2) (124, 125, 181). In contrast, inhibition of mutagenity of BP (97, 183), Trp-P-1 and Trp-P-2 by harman and norharman has also been reported (95). Chang et al. (38) have found that harman and norharman decrease the incidence of spontaneous and ultraviolet-light-induced mutations in cultured Chinese hamster cells.

Several mechanisms have been considered for the "comutagenic activity" of harman and norharman: alteration of the extracellular metabolic activation of mutagens; alteration of the bacterial metabolism involved in mutagenesis or a more direct action such as interaction of comutagens with DNA (68, 181). However, these two β-carbolines have been found rather to inhibit BP metabolism and the binding of BP metabolites to DNA in vitro (97, 183). Although norharman and harman have been reported to intercalate into DNA

in vitro, causing the unwinding of the double helix (68), this intercalation does not seem to affect the affinity of Trp-P-2 (a potent mutagen) for DNA (95). Lau and Luh (95) have pointed out that the potentiating effect of the comutagens on mutagenesis under unfavourable enzymatic conditions may be an artifact of the assay method.

PHARMACOLOGICAL EFFECTS IN ANIMAL EXPERIMENTS

General pattern of effects

When, in 1935, Gunn (64) described the general pattern of the actions of β-carbolines, he claimed these drugs to be quinine-like: they showed clonic convulsant action followed by depression of the CNS, contracture of frog's isolated voluntary muscle, relaxation of most smooth muscles (but contraction of uterine muscle), a depressant action on cardiac muscle, a local anaeasthetic action, and toxic action on protozoa. His studies on structure-activity relationships, however, already showed rather large differences in the actions of different β-carbolines and even though quinine and β-carbolines may have biochemical similarities (inhibit ion transport), we can now say that not all the effects of β-carbolines are quinine-like.

Other long-known effects of harmala alkaloids (99, 103) include, for instance, tremor, nystagmus, stereotyped behaviour like padding with front paws, increased perspiration, salivation, lacrimation and diuresis, and changes (often a fall, but sometimes a rise) in rectal temperature, heart rate and blood pressure. Although various effects are described in a certain conditions in a particular animal with a certain β-carboline, only a few of them, like the tremorogenic action and some behavioural effects, have been more intensively examined and attempts have been made to relate them with the biochemical effects. Several other effects have recently been intensively started to research.

Tremor

The symptoms caused by harmaline and some other β-carbolines in man have regularly included tremor. In animal experiments the fine generalized tremor (at 6—12 Hz) caused by harmaline and harmine, which often occurs together with nystagmus and before tonic-clonic convulsions, has been studied by several investigators (1, 2, 19, 53, 67, 70, 93, 105, 140). Tremor has also been occasionally noted among the effects of other β-carbolines including THBCs (3, 12, 31, 144), and Zetler et al. (191) have described in mice some structure-activity relationship studies on this effect.

Site of tremorogenic action. The main site of tremorogenic action of harmaline seems to be the inferior olivary neurons (93) where an increased rhythmic activation at intervals of about 100 msec has been demonstrated (22, 101) during the tremor. The activation is transmitted via the climbing fibres to the Purkinje cells and the cerebellar nuclei (44, 102). The tremor can be abolished by destroying the cerebellar climbing fibres with 3-acetylpyridine (159).

In a [^{14}C]deoxyglucose-uptake study, harmaline induced an increased uptake in medial and dorsal accessory olive of kittens, suggesting increased activity in these sites, but the uptake by Purkinje cells did not seem to change (18). However, the inhibitory action of harmaline on Na^+-dependent sugar transport may influence the results in this type of study. The exact site of tremorogenic action of β-carbolines (inferior olive or some input to it) and, particularly, the involvement of different neurotransmitters are still unknown, and even the results obtained with harmaline and harmine may not always be identical (72). Stereotactic injections of harmine and lesion experiments have given partly conflicting results, suggesting perhaps the involvement of several parts of brain and more than one neurotransmitter.

The developmental studies show that in rats harmaline, in contrast with the cholinergic tremorogens, does not cause tremor before considerable maturation of olivary and cerebellar functions, which occurs at about 14 days after birth (70, 88, 136). This might be due to maturation of olivary receptors, the establishment of electrotonic junctions between the dendrites of inferior olive neurons (101, 167) or the development of the relevant inputs to the inferior olive.

Possible role of benzodiazepine-GABA receptors. In the rat the tremor seems to be associated with the increase of cerebellar cyclic guanosine monophosphate (cGMP). Both the tremor and cGMP increase were antagonized with diazepam (106, 107) and some inhibition of [^{3}H]flunitrazepam binding was found in vitro with the maximum harmaline concentrations which occurred in the brain during heavy tremor. Therefore Rober

...n (141) have suggested that the tremor could ...e due to the action on benzodiazepine recep... ...rs (»β-carboline receptors»). On the other ...and, harmaline-induced tremor and increase ...f cGMP may also be abolished with a longer ...cting potent prostaglandin E_2 derivative ...(S)-16-methyl PGE_2 (21). In rabbits both ...rmine-induced tremor and the desynchro... ...zation in EEG and the simultaneously in... ...ced 10 c/s synchronous waves found in ...bro-olivo-cerebello-rubral loop are anta... ...nized by diazepam but the synchronous ...aves at the level of red nucleus are diaze... ...m-resistant (154, 177). In unanaesthetized ...rarized rats and rabbits diazepam decreased ...ontaneous simple spike activity but it had ...tle effect on harmaline-induced complex ...ike activity of cerebellar Purkinje cells ...4). It is interesting that [^{3}H]harmaline in ...onkey brain is first during the period of ...emor and convulsions highly concentrated ...gray matter (73), but later during CNS de... ...ression mainly in the white matter. Benzo... ...azepine receptors are concentrated in the ...y matter, but so are many other receptors.

The most potent tremor-inducing β-carbo... ...es are DHBCs or fully aromatic BCs, which ...o have a high affinity for benzodiazepine ...nding sites (7, 146). On the other hand, ...HBCs, which show a very low affinity on ...Z binding sites, also have tremor-inducing ...operties, while harmol and harmalol, which ...ow a moderate affinity, may not cause ...emor (64) and β-carboline carboxylic acid ...yl ester, which has the highest known ...finity on BZ receptors (25), failed to pro... ...ce any signs of tremor in mice (176). Thus ...simple benzodiazepine receptor action is ...obably not the cause of tremor.

GABA-receptors seem to be close to the ...nzodiazepine receptors (for ref. see 40) and ...me studies connect the effects of harmaline ...GABA. Harmaline inhibits the uptake of ...ABA by synaptosomes (182), it also blocks, ...obably presynaptically, in less than 10^{-4} ...ol/l concentrations GABA-mediated in... ...bitory postsynaptic potential in grayfish ...retch receptors. This cannot easily be ...rrelated to the effects on mammalian ben... ...diazepine-GABA receptor systems. In ...mmals the effects of β-carbolines on ...ABA-ergic systems may be due to the ...tions on benzodiazepine receptors, which ...e thought to regulate the sensitivity of ...ABA receptors through »GABA-modulins» ...).

Possible role of 5-HT, dopamine, noradrenaline and acetylcholine. Some studies suggest the involvement of serotonergic neurons in harmaline and harmine tremor. The serotonergic inhibitory inputs to the olive are sensitive to harmaline (69, 162, 185). On the other hand, some results, such as the effect of 5-HT uptake inhibitor quipazine (91) and the opposite effects of 5-HTP on harmaline and harmaline tremor in rats and monkeys (57, 85, 86), are difficult to interpret; and the failure of a synthesis blocker p-chlorophenylalanine to modify the tremor would seem to indicate that the role of 5-HT is not very essential. The increase of serotoninergic input to the olive, however, seems to induce similar rhythmic bursts to those obtained with harmaline (162).

Zetler et al. (191) have shown in mice that both in harmala and iboga alkaloids the methoxy group, particularly in the 7-position, enhances the tremorogenic potency, whereas hydroxy-group decreases it. The presence or absence of a double bond as well as the lipid solubility seemed to be of minor importance. The potency does not seem to correlate with the inhibition of 5-HT uptake or to the binding on benzodiazepine receptors.

The enhancement of harmine and harmaline tremor by reserpine or tetrabenazine (1, 85) and its reduction by dopaminergic drugs such as apomorphine (85) suggest that dopamine antagonism may be involved in the tremorogenic action as well as in other »extrapyramidal» actions of β-carbolines. Also, the structure-action relationships of tremorogenic potency (191) and the antidopaminergic actions of β-carbolines (84) may have some relation. Because harmaline has been shown to decrease striatal dopamine while 5-HT concentration increases (139) the ratio of these amines to each other may be more important than the presence and concentration of any one of them. The simultaneous changes of cGMP, however, seem not to be mediated by dopamine. In rats with kainic-acid-induced lesions of dopaminergic target cells in striatum with decreased striatal cGMP, the action of harmaline on cGMP was the same as or greater than the controls (22).

The increase of brain NA content with L-threo-3,4-dihydroxyphenylserine or with intracerebral NA injections suppress harmaline-induced tremor in rats and mice (85, 188, 189) and a possible involvement of the ascending noradrenergic neurons from locus coeruleus to the striatum and cerebellum has been suggested (189). On the other hand,

studies with a synthesis blocker α-methyl-p-tyrosine (1, 57, 85) and with α- and β-receptor blockers (1, 41, 85) suggest that the decrease of adrenergic tonus does not modify harmine or harmaline tremor.

While some results may suggest the involvement of acetylcholine (ACh) on the harmaline tremor, most of the data available suggests that its role is not essential (for references see 72).

Convulsions

In addition to tremor, clonic convulsions as major effects of harmine and harmaline in different mammals were described as early as 1895 by Tappeiner and later by Flury (52), Gunn (64) and many others. In 1935 Gunn (64) also described structure activity relationships between 1,7-MeO-1-Me-BC, 7MeO-1-Me-DHBC, 1-Me-THBC, THBC and a series of synthetic harmol-O-derivatives and found that both THBCs, DHBCs and BCs in variable doses caused convulsive action followed by central depression when lacking radicals (THBC) or when 1-methyl of 7-methoxy (7-alkoxy) was substituted, but the 7-OH-derivatives (harmol and harmalol) showed only signs of central depression.

The structure-activity relationships of the convulsive action do not seem to correspond to those of MAO-inhibition or amine uptake inhibition. The mechanism of the convulsive action may be partly connected to in vivo binding to benzodiazepine receptors (Airaksinen and Saano, unpublished). Correlation of the convulsive dose and in vitro binding is not good. However, pharmacokinetic differences (OH-groups decrease the transport to the brain) and other partly antagonistic actions might explain the differences. It remains to be shown if the signs of CNS depression correlate with the binding to opiate receptor sites. Both actions seem to require an OH-group in the ring. The inhibition of 5-HT uptake and the increase of brain 5-HT concentration may result in the anticonvulsive properties. 6-MeO-THBC has been shown to inhibit audiogenic and electroconvulsive seizures in mice (32), possibly through increased serotonergic action. It is interesting that the pineal gland has a high concentration of 6-MeO-THBC (83) and pinealectomized animals show epileptic EEG syncronization and a lowered seizure threshold (for ref. see 11), but melatonin also has an antiepileptic effect (11).

Temperature regulation

β-Carbolines in high doses have significant effects on the body temperature. A fall in temperature is the most common effect (3, 29, 30, 144, 145, 153, 185) and this is quickest and most prominent after intracisternal (28, 144) or intrahypothalamic (3) administration.

The effect, however, varies greatly with the species. Thus harmine raises the temperature in mice (191), and harmaline raises it in rabbits (92), although both compounds lower it in rats. 6-MeO-THBC administered to mice only lowered the temperature while in rats i.p. it was increased, and intrahypothalamically first lowered and then elevated the temperature, this effect being similar to that of 5-HT (3). Studies with reserpine and the synthesis blockers of 5-HT and catecholamines suggest an involvement of both 5-HT and NA on the hypothermic and hyperthermic effects of β-carbolines (for ref. see 72). In our study (3), 6-MeO-THBC increased both the hypothermic effects of reserpine in mice and its hyperthermic effect in rats.

Analgesia

Some β-carbolines have analgesic effect. The analgesic potency of THBC has been preliminarily reported to be about 1/10 that of morphine. It may be due to its 5-HT-ergic effects because it can be blocked by 5-HT antagonists (145). It seems, however, that compounds with OH-group have the clearest analgesic action, for example, 6-OH-THBC is more potent than THBC (144), and a binding on opiate receptors (7) is probably involved.

Effects on sucrose and alcohol preference

The effect of a »serotonergic» β-carboline on taste has been demonstrated by Nance and Kilbey (126), who showed that the increase of (2 %) sucrose preference caused by p-chlorophenylalanine pretreatment in rats can be abolished either by 5-HTP or 6-MeO-THBC in doses which correct the brain 5-HT depletion.

The studies on the effects of some THBCs on alcohol preference of rats have given conflicting results. A single high peripheral dose of THBC, 1-Me-THBC or 6-MeO-1-Me-THBC in rats lowered alcohol preference in the free choice situation (56, 116). This was thought to result from the inhibition of alcohol dehydrogenase and or an increase of brain 5-HT level. However, Myers and coworkers (122, 123) have reported that THBC significantly increases alcohol preference when given in small repeated or single daily doses intracerebroventricularly (i.c.v.). The effect

continued for weeks after the end of THBC administration. They used a rat strain with a low initial alcohol intake. This has been partly, but not fully, confirmed by Dietrich and Erwin (43). On the other hand, Holman et al. (77) have found that 6-OH-1-Me-THBC, when administrated daily i.c.v. for 11 days, decreased voluntary alcohol consumption in rats with a rather high base-line alcohol intake.

We have made preliminary tests in two strains of rats to determine the effect of THBC and 1-Me-THBC on alcohol preference. The drugs were continuously infused i.c.v. with Alzet® minipump for 12 days, and with low dose we did not find significant differences from the controls, but a higher dose seemed to increase alcohol preference. All of these studies are based on alcohol consumption rather than on blood alcohol levels in the rats. Thus the possible differences may have been influenced by taste differences and, as stated recently (39, 160), one cannot say whether the rats in any of these tests drink to get drunk.

Appetite, fluid intake

THBC has a bitter taste, and this may have decreased the fluid intake when THBC was given in the drinking water. The appetite also decreased in a concentration-dependent manner between the 3rd and 12th days (145) but after that the rats ate like the controls. Consequently, the body weight first fell but later increased normally. Although the decrease of dry food intake may be secondary to the decreased fluid intake, it has been suggested as resulting from increased serotonergic action. However, 6-MeO-THBC in nontoxic doses (in drinking water or given daily i.p.) had little effect on food or water intake of rats, except for a slightly decreased water intake when starting with higher concentrations (3). The vomiting effect of β-carbolines, best shown in man, may also play a part in suppressing appetite.

Motor activity, aggressivity and stereotypic behavior

As with the tremorogenic and convulsive effects, the effects on motor activity also differ largely between different β-carbolines. Earlier papers usually divide the effects only with respect of motor exitation and depression (e.g. 64), but Fuentes and Longo (53) have pointed out three types of effect. The excitation caused by harmine and harmaline in rats and rabbits is expressed before tremor and convulsions as an increase in the motility and also in the frequency and voltage changes in the EEG at the cortical and hippocampal levels. In contrast, some convulsive β-carbolines, e.g. harman (1-Me-BC) and norharman (BC) may in nonconvulsive doses decrease the motor activity by producing catatonic states. Some β-carbolines like harmol (7-OH-1-Me-BC) and 1-Me-THBC induce a decrease of motor activity and in high doses a paralysis in rats. The rather toxic 6-methoxy-pyridoxalyl-THBC has also been reported as causing paralysis of the hind legs as a short-lived primary effect of nonlethal doses in rats and mice. Long lasting effects have also been studied in mice (173). The treated mice behaved normally when alone but when put together with others they exhibited first agitation with trembling and rapid tail rotation and then started repeated biting attacks. This aggressive behaviour lasted for at least three weeks. The mechanism of this long effect is unknown, though antagonism of B_{6}-vitamin was suggested. In our studies, however, 6-methoxy-DHBC also seemed to increase the aggressivity of rats during handling, and aggression with biting attacks have been described after harmine administration in dogs (99). Several β-carbolines may, like a related alkaloid ibogaine and other hallucinogens (90), also prevent different types of induced aggressivity in animal experiments.

The decrease in motor activity caused by THBCs can be found with small doses when administered i.c.v. to rats (60) or intracisternally to mice (144). High doses of THBCs like 6-MeO-THBCs themselves cause the »serotonergic» stereotyped behavior (3), but the decrease of motor activity by β-carbolines has been suggested as being due to the antidopaminergic action. Many β-carbolines are effective inhibitors of the stereotyped behaviour caused by dopaminergic drug apomorphine (84, 133, 145, 184), and they inhibit some effects of dopamine releasing drugs, e.g., the group toxicity of amphetamine (3) and the stereotyped hyperactivity of β-phenylethylamine (84).

Westerman et al. 184) demonstrated that apomorphine-induced motor activity is antagonized by harmine in rats. THBC has then been shown to antagonize apomorphine-induced stereotyped licking (145) and biting (84) and, in rats with unilateral lesions of the forebrain bundle, the apomorphine-induced contralateral turning response (145). Supersensiti-

vity to apomorphine has been reported after chronic administration (145). The apomorphine antagonism of harmine corresponds chronologically with the increase of 5-HT content in the striatum and Westermann et al. (184) have shown that harmine antagonizes the increased apomorphine hypermotility induced by p-chorophenylalanine pretreatment or by injecting 5,6-dihydroxytryptamine into the media raphe nucleus. These seemed to be due to the dopaminergic-serotonergic interaction. According to a recently published paper of Pannier and Rommelspacher (133), however, the pretreatment of rats with two high doses of p-chlorophenylalanine or a lesion of the raphe nuclei decreased apomorphine-induced licking, and small doses of THBC neutralize this effect while high doses cause catalepsy. These are interpreted as resulting from the combined serotoninergic and direct antidopaminergic effect of THBC.

We studied the structure activity relations of some β-carbolines as antagonists of apomorphine-induced stereotyped biting and phenylethylamine-induced hyperactivity in rats (84). In both tests 6-MeO-DHBC was more active than the THBCs studied. No correlation seemed to occur with the 5-HT uptake inhibition in vitro. Because 6-MeO-DHBC and harmine are bound to the benzodiazepine binding sites (7, 146) and because the GABAergic neurons may regulate striatal dopamine release (40, 55) the effect on benzodiazepine-GABA receptor systems may also be a part of this action.

Effects on reinforced behaviour and shock avoidance

Most β-carbolines seem to distrupt reinforced conditioned lever pressing for food, milk or water in rats (decrease in the pressing rate). Some structure-activity relationships among a group of 1-methylated β-carbolines were briefly reported by Taborsky and McIsaac in 1964 (174). All these, including 6-OH-1-Me-THBC, which may only poorly penetrate the blood-brain barrier, effectively inhibited variable-interval positive-reinforcement operant behaviour of rats. A later paper of McIsaac et al. (111), which describes the effects of some 6-methoxy-β-carbolines with fixed-interval reinforced conditions, showed that the nonsaturated 6-MeO-BC and 6-MeO-DHBC were more active than the corresponding saturated compound 6-MeO-THBC, while the N-acetyl derivative of 6-MeO-THBC was inactive. There was a good correlation between this behavioural effect and MAO-inhibition and the increase of brain amines. The effects of 6-MeO-THBC, which is a typically »serotoninergic» β-carboline, was also studied in stimulus-controlled variable-interval reinforcement conditions and the substance was found to distrupt the stimulus control in a similar way to that caused by the known hallucinogen psilocybin (4-OH-tryptamine) (111). According to Buckholtz (31), 6-MeO-THBC also produces retention deficit for one-trial passive avoidance in rats.

It has remained unclear how much these effects depend on brain 5-HT. Winter (180) showed, however, that the harmaline-induced decrease in the conditioned lever pressing rate in a fixed-ratio schedule was not significantly altered by centrally or peripherally acting 5-HT antagonists. Harmaline, on the other hand, antagonizes the effects of tetrabenazine on the performance of rats under different schedules of conditioned behaviour (24, 113), probably by alleviating the decrease of transmitter amines. In rats on the Sidman avoidance schedule tetrabenazine reduces the rate of reinforcement responses; harmaline pretreatment delays the onset of this reduction and may induce an increased response rate (24).

Endocrinological effects

Compounds acting on hypothalamic neurotransmitters may indirectly influence the synthesis and release of hypothalamic and pituitary hormones. Of β-carbolines, only the hormonal effects of 6-MeO-THBC have been studied to any extent.

6-MeO-THBC has significant hormonal effects which in some degree resemble those of melatonin and other pineal 5-methoxyindoles. It also occurs in high concentrations (several μg/g) in the pineal gland of chicken and cock (our mass spectrometrical observations, 83), i.e. in similar concentrations to those of melatonin. Furthermore, we found that its concentration in the pineal has a circadian rhythm and the concentration seemed to decrease with age. The other sites where it is known to occur, the adrenals and arcuate nucleus in the hypothalamus, may also be connected with hormonal function.

Our preliminary studies on 6-MeO-THBC showed that its chronic administration to young male rats inhibited the development of genital organs (5). In female rats in high doses (< 25 mg/kg/day) it made the diestru

longer or totally abolished the estrus, in a smaller dose it caused only weight changes in the endocrine organs. While the weights of pituitary, ovaries and uterus decreased, the adrenal weight increased during the subacute treatment. The adrenal weight similarly increased in mice (3). Meyer and Buckholtz (118) found an increase in plasma corticotropin concentration after the administration of various β-carbolines (THBC, 6-MeO-THBC, BC, 1-Me-BC and 6-MeO-BC) and Fang et al. (39) an increase in plasma prolactin concentrations in rats after an acute 6-MeO-THBC administration.

The increase of prolactin excretion seemed to be due to the increased 5-HT effect (33, 43). On the other hand, the increase of corticotropin was not prevented by a 5-HT synthesis inhibitor p-chlorphenylalanine or by 5-HT antagonists, although a 5-HT uptake inhibitor fluoxetine increased its effects (119). Whether other neurotransmitters or specific own receptors are involved is not known. If the endocrinological effects of 6-MeO-THBC are caused by its serotonergic action alone, then all the THBCs which effectively inhibit 5-HT uptake — or perhaps those β-carbolines which increase the ratio of effective 5-HT/dopamine — will have similar effects.

The concentration of 6-MeO-THBC in the pineal gland (83) is much higher than the levels reported in adrenals and brain of rats (87). It remains to be shown whether its occurrence in the arcuate nucleus and adrenals represents the presence there of some receptor sites and whether it participates in the regulation of aldosterone secretion, namely, whether 6-MeO-THBC is the »adrenoglomerulotropin» of Farrell and McIsaac (29).

EFFECTS IN MAN

Existing knowledge of the effects in man of carbolines, particularly THBCs, is scanty and fragmentary, although man has used carbolines for treating disease as well as for hallucinogenic purposes. The ancient Greek, Indian and Arab physicians used the seeds of Peganum harmala as drugs. In Greece the drug was used mainly to treat eye diseases, while in India various diseases were treated for example the seeds were used as analgesics for lumbago and menstruation. Other uses were as an aphrodisiac, to increase milk secretion, and to »purify blood». In ancient Arab medicine they were used an anthelmintics and for their effects on the CNS. Matthiolus described in his New-Kreuterbuch 1629, the emetic, diuretic and antidepressive effects of this »Fremde Harmalraute» (ref. in 103). Single harmala alkaloids have been used in clinical trials since the start of this century (12, 52, 62, 63, 64, 98, 99, 103). The description of the results of the experiments, however, has usually been limited to the symptoms or disease examined and possible side effects have been poorly described and sometimes only the preliminary results have been published. Furthermore, human trials with a single compound are limited to some harmala alkaloids; so far as we know, no experiments in man have been carried out with those THBCs which seem to be physiological constituents of the human body.

Studies on the hallucinogenic and other CNS effects

Although the ability of harmine (7-MeO-1-Me-BC) to cause colored visions and hallucinations was known earlier (for ref. see 103), the study of Pennes and Hoch in 1957 (134) was probably the first one dealing with the genuine hallucinogenic property of a β-carboline. They found harmine to be clearly hallucinogenic if given i.v. in high doses, the threshold being 150—200 mg; 4.8—6.4 times higher doses were required per os. On the other hand, other central and peripheral symptoms (bradycardia, difficulty in focusing the eyes, tingling, hypotension, cold extremities and lightheadedness) were always present after an i.v. dose of 35—45 mg (0.5 mg/kg) of harmine in a later study of Slotkin et al. (165). Both Pennes and Hoch and Slotkin et al. described harmine as causing hypotension, but harmine and harmaline have also been described as increasing the blood pressure with a »camphor-type» action related to tonic-clonic convulsions (103).

In 1928 Lewin described symptoms occurring after s.c. doses 20—200 mg of »banisterine» (harmine). The highest dose caused particularly heavy vomiting and severe tremor, starting with »intern tremor», buzzing in the ears, cold sweating, dysphoria and a drop in heart rate. The symptoms included some changes in the perception of colours but not of figures, increased sensitivity to sounds and a change in the taste of a cigarette, but there were no real hallucinations. Smaller doses of harmine taken by Lewin himself initially caused a slight euphoric feeling of warmth

and sedation, followed by tremor, involuntary movements of the fingers and a feeling of ants running over the skin. Similar symptoms were described by Pennes and Hoch (134) and in addition visual hallucinations occurred in 5/11 patients, but the development of bradycardia and hypotension limited the dose. They described the tremor as being of the extrapyramidal type. Their patients also described »waviness» of the environment, »sinking» sensations of the body, humming and buzzing noises (but no voices), and subjective numbness, accompanied by objectively reduced sensitivity to light touch and pinprick. In the same study nalorphine caused some of similar effects.

The largest human studies on the hallucinogenic and other effects of β-carbolines have been carried out by Naranjo (127). The largest group (= 31) of volunteers in his tests received harmaline (7-MeO-1-Me-DHBC) and only the effects of this drug were thoroughly described but the study also included harmine (7-MeO-1-Me-BC), tetrahydroharmine (7-MeO-1-Me-THBC), 6-methoxyharmalan (6-MeO-1-Me-DHBC) and 6-methoxytetrahydroharman (6-MeO-1-Me-THBC). Thus Naranjo was able to give some structure-activity relations of the hallucinogenic effect for different β-carbolines and compare them with the actions of other hallucinogens.

Some physical sensations — for example, paresthesia of the hands, feet and face, often followed by numbness — always occurred with harmaline intoxication. Other typical symptoms included nausea and sometimes intense vomiting, chest discomfort, pressure in the head, dizziness and general malaise (which could vary in relation to certain thoughts and stimuli), enhancement of certain sensations (noises seemed pronounced and generally troublesome), passivity to physical movements, withdrawal from external world, and willingness to lay down. With eyes closed the subjects had vivid, coloured imagery often with particular themes and dreamlike sequences. When the subjects had their eyes open they mainly described illusions and other visual phenomena, such as perception of double or multiple contours sometimes with hallucinations occurring typically as images on walls or ceilings, while perception of the principal environment and the sense of time were unaltered. These images were usually understood by the subject to be unreal but sometimes they seemed realistic enough, with one man seeing »a cat climbing a wall, then turning into a leopard», when even the cat did not exist.

All the volunteers receiving harmaline had on different occasions taken mescaline and some of them LSD as well, and all described the effects of harmaline and other β-carbolines as being quite different from those of mescaline or LSD. The physical sensations were more typical of harmaline than of mescaline, and distorsions of forms and enhancement of sense of depth, perception of movement, colours and aesthetic qualities, all of which are typical for LSD, were not described for harmaline. In general, harmaline had much less effect on emotions and thinking, and Naranjo (127) states it to be »more of pure hallucinogen». According to Shulgin (158), if used in conjunction of other psychedelic drugs harmaline prolongs and modifies their effects.

Differences in the actions of various β-carbolines seemed to be smaller (127). Harmine and harmaline have caused similar visual hallucinations, but when the threshold for the hallucinogenic effect for harmaline was 1 mg/kg i.v. or 4 mg/kg by mouth, twice as much harmine was required and it seemed to cause less withdrawal and lethargy. In one person tetrahydroharmine was similarly hallucinogenic when given in three times the dose of harmaline.

The 6-methoxy-derivatives 6-MeO-1-Me-DHBC and 6-MeO-1-Me-THBC also showed similar effects and were slightly more potent than the corresponding 7-methoxy-derivatives harmaline and 7-MeO-1-Me-THBC (tetrahydroharmine). They seemed, however, to be »of less hallucinogenic nature in the strict sense of the word, their effect being more akin to a state of inspiration and heightened introspection».

Therapeutic trials

Gunn (64) has reviewed the therapeutic trials with β-carbolines carried out with different indications by English speaking scientists before 1935. In addition to this, clinical observations and the use of pure harmala alkaloids and seeds of Peganum harmala have been described in early German literature (65, 66, 98, 99, 103).

It is interesting that harmine (7-MeO-1-Me-BC), a convulsive and tremor-inducing BC (99, 103), and harmalol (7-OH-1-Me-DHBC), which causes CNS depression (63), have shown some therapeutic effect in Parkinson's disease, being described as decreasing rigidity

In 1665 Mattiolus stated that Peganum harmala was useful for melancholics (103). Later an antidepressive action has been attributed to some β-carbolines like 6-MeO-THBC because of their properties of MAO inhibition and 5-HT uptake inhibition, but we have not found any clinical studies on the antidepressive effects of β-carboline compounds.

Harmol and propyl-harmol were tested as antianginal drugs by Bramwell et al. in 1933 because of the ability of some β-carbolines to dilate coronary vessels of the isolated mammalian heart (28). Only limited relief of acute pain was reported after s.c. injection. Although several β-carbolines cause uterine contraction in rabbit in situ, the clinical trial on the use of harmol (7-OH-1-Me-BC) in the induction of labor in parturients (62) did not show much effect.

Because of other quinine-like effects of β-carbolines, including the effects on protozoa in vitro, harmaline and harmine were tested against human malaria, while 7-OH-1-Me-DHBC, 7-OH-1-Me-BC and three synthetic derivatives of 7-OH-1-Me-BC were tested against bird malaria, but the preliminary results were disappointing (64). In a recent study extracts from Peganum harmala have given promising results in certain dermatoses (47) of an inflammatory nature. The extracts are claimed to possess antibacterial, antifungal and antipruritic properties, and probably also an antiprotozoal action, but it is not known whether β-carbolines or other constituents in the extracts are responsible for these effects.

GENERAL COMMENTS

Possible physiological functions

Although there is good evidence that some β-carbolines are normal metabolic constituents in man as well as in animals, the role of these compounds is still obscure. However, many pharmacological studies suggest a role as neuromodulator for these compounds. Some β-carbolines, particularly the THBCs formed from formaldehyde, fulfil the common properties of neurotransmitters and neuromodulators (36): mechanisms for their synthesis in CNS has been shown, they seem to accumulate in the nerve endings, K^+ induces their release although the release with nerve stimulation has not been demonstrated, and they can be inactivated by an active uptake mechanism. No specific receptors for THBCs have been found but the nonsaturated β-carbolines, of which only 1-Me-BC has been shown in the mammalian body, seem to be agonists of the BZ receptors or BZ recognition site in the GABA-BZ receptor complex. These BZ receptors may not transmit depolarization or hyperpolarization but they do modulate the effect of GABA. This property and particularly the effects of β-carbolines on the uptake, release and metabolism of 5-HT and also of catecholamines suggests a neuromodulator function for those β-carbolines which occur in CNS. β-Carbolines in the group seem to fulfil all the criteria of neuromodulators presented by Barchas et al. (16), but so far not all of these have been demonstrated for any single β-carboline compound shown to occur normally in the body.

Inhibition of 5-HT uptake may be the major biochemical effect of THBCs, which have unquestionably been shown to occur in mammals, and a regulating effect on the 5-HT-ergic system may be one of the most important effects in vivo. However, effects on the catecholamines may also occur. A selective and potent inhibition of MAO-A has been shown particularly by the nonsaturated β-carbolines, both in vitro and in vivo, and 5-HT and NA are the substrates for MAO-A.

6-MeO-THBC have been recently identified in the pineal gland of chicken and male fowl (83), as well as in the brain and adrenals of rats (17); this substance seems to have a melatonin-like circadian rhythm in the pineal gland. Thus its participation in the regulation of biological rhythms is possible. Furthermore, the effects of 6-MeO-THBC on genital organs (3, 5), as well as on the secretion of prolactin (43) and corticotropin (118), may indicate a hormonal function. If 6-MeO-THBC can be verified as a significant pineal hormone it also needs a simple name, and we suggest pinoline (the pineal β-carboline). It remains to be shown if the 1-methylated β-carbolines have similar hormonal actions and whether this could partly cause the hypogonadism and other endocrine disturbances found in chronic alcoholists.

Involvement in CNS diseases

Attempts have been made to relate β-carbolines to mental diseases, particularly with schizophrenia, because they have hallucinogenic properties. As an hypothesis it is attractive, but the β-carboline concentrations needed to produce hallucinations are high when compared with the concentrations which are reasonably possible in vivo. Ad-

ditionally the »hearing of voices» is not typical as is the case in schizophrenic hallucinations. On the other hand, several investigations have shown the antidopaminergic properties of β-carbolines. Thus, if dopamine hypothesis is valid for any type of schizophrenia, the β-carbolines in the body may protect against such mental disorders rather than aggravate or induce them.

We think that the symptoms that Naranjo (127) and others described in man as attributable to β-carbolines are not like the symptoms of schizophrenia, but are similar to those found during alcohol withdrawal (51, 61, 81) and to an extent to those during the withdrawal of other sedatives (81). Most of them probably occur during the tremulous hangover after an relatively acute intake of a large quantity of alcohol, others resemble the symptoms of alcohol hallucinosis or delirium tremens. If, however, we compare them with the different symptom groups (factors) of the alcohol-withdrawal syndrome described by Gross et al. (61) the β-carbolines seem to cause in particular factor 1 disturbances (of perceptual and cognitive systems) with the assumed localization in cortical structures and sensory receptors, and factor 2 (affective) disturbances localised in the limbic systems, with factor 3 disturbances of the brain stem being the least prominent. This agrees with the supposed major sites of action of β-carbolines on serotonergic systems and on benzodiazepine receptors. It has even been suggested (127, 175) that the visual symptoms caused by β-carbolines have a retinal origin, because in bovine retina 6-MeO-THBC both effectively inhibits 5-HT uptake and potentiates K^+-induced release of 5-HT (175), and in cats given harmaline the changes in the electroretinogram (increased alpha waves and decreased beta waves) are apparent before any changes are observed in the brain cortex (127).

Any connections between β-carboline effects and the symptoms of delirium tremens and hangover remains hypothetical, because so far only the effects of 7-methoxylated β-carbolines, harmaline and harmine, which are not formed by the mammalian body, have been sufficiently studied and described to allow comparisons to be made. Evenso, this link is tempting because of our findings (9) that a significant concentration of 1-Me-THBC in human blood platelets and plasma after acute alcohol intake occurs at the time of maximum hangover. This compound may not, however, be formed in brain because acetaldehyde poorly penetrates the blood-brain barrier (100) and the brain concentration of 1-Me-THBC was very low in our preliminary studies in rats (8). The relation of β-carbolines to the withdrawal syndromes of other sedative drugs is even more hypothetical, although an increase of physiological antagonists to BZs (receptor agonist?) would be a logical rebound phenomenon after a long use of BZs.

Two β-carboline derivatives have been found as alcohol metabolites in man and in rats. The occurrence of 1-Me-THBC has been reported by several investigators (20, 135, 148) and that of a wholly aromatic derivative (1-Me-BC) by one group (148). On the other hand, the latter has also been reported as a normal constituent in human blood platelets. The importance and the role of these compounds in alcohol withdrawal and dependence remains to be shown. Nevertheless, the binding of β-carbolines on specific binding sites (benzodiazepine and opiate receptors) may be connected with alcohol dependence. Furthermore the β-carbolines in tobacco smoke (BC and 1-Me-BC) show activity on benzodiazepine receptors. Thus, their participation in »tobacco dependence» cannot be excluded.

It is also tempting to suggest that β-carbolines participate in the symptoms of stress and anxiety because of their actions (some are antagonized by anxiolytic BZs) and their site in adrenals and brain. Clover, Bhattacharya, Sandler and File (unpublished) have found a MAO-inhibitor in the ethyl acetate extract of rat urine which probably has a β-carboline structure, and which largely increases with cold immobilization stress, an increase that can be prevented by BZs. However, even if an increased amount of β-carbolines are formed, particularly those β-carbolines which effectively inhibit MAO, act on adrenals and/or are bound by BZ receptors, their synthesis may be secondary to other more primary changes. Similarly, although β-carbolines induce tremor and convulsions, nothing is known about their concentrations in patients with Parkinson's disease, essential tremor, epilepsies, or other neurological diseases.

In conclusion we can say that more research is needed before any neuromodulatory, endocrine or other physiological roles for the β-carbolines can be confirmed. The same is true for their possible involvement in neurological, psychiatric or other diseases, or the

...ales. Many effects of different β-carbolines are known but we know neither the effects in man of the physiologically occurring β-carbolines nor even which of these compounds occur physiologically. So far only such THBCs which are formed by formaldehyde and acetaldehyde are found in mammalian tissues. The possible synthesis and effects of β-carboline derivatives formed by other aldehydes including indoleacetaldehydes is one interesting question. Further biochemical and animal studies on the effects of β-carbolines are necessary and controlled studies on the significance and effects in man of those β-carbolines occurring in the body are particularly needed.

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